5/19/88

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MAY 19 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Naled - Addendum to the Rat Chronic Study S-1802, Submitted Under Accession No. 404189-01
EPA Registration No. 239-1633

TB Project No.: 8-0514
Caswell No.: 586

FROM: Irving Mauer, Ph.D. 05/18/88
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5/19/88

Registrant: Chevron Chemical
Richmond, CA

Request

In response to a request by the Office of Compliance Monitoring (OCM) dated November 5, 1987 (from the Lab Data Integrity Assurance Division), the registrant has submitted under cover of November 20, 1987, additional data on the test material and analysis of gavage suspensions used in the Dibrom Rat Chronic Oral Toxicity/Carcinogenicity Study, S-1802 (MRID No. 00128701), conducted by Bio-Research Laboratories (BRL), Senneville, Quebec (BRL Project No. 9394, report dated June 4, 1984).

In their November 20 response, Chevron also explained that analyses on dose formulations were initially conducted at BRL, but taken over by Chevron 8 months later because of

H74

a lack of GLP (revealed by sponsor audit); both sets of analytical data are included in the Addendum submitted. Chevron responded to additional queries by OCM regarding the test chemical in a letter dated December 1, 1987, by:

1) Reaffirming the stability of Lot SX-1278 used in this rat study, since a retained sample of test material assayed at 91.6%;

2) Providing a full description of the chemical composition of the formulation (see below) in the submission of November 20, 1987 (as Appendix II); and

3) Stating that Lot SX-1278 used in this study was a "subsample" from a commercial lot manufactured by Shell Chemical Company (Shell Lot No. 01-AMR-011) for Chevron and was "used as received and not subjected to any modification."

The Submission, EPA Accession No. 404189-01

The additional data submitted as an Addendum to S-1802, Lifetime Rat Chronic Study, are as follows:

Appendix I: Dosage Formulation Preparation Procedures--The results of mixing and stability (up to 3 hours) studies demonstrated that substantial degradation of naled occurs at room temperature, but when prepared and maintained appropriately (refrigerated in dark-brown bottles), the three dose levels assayed at 88 to 94 percent of nominal. This analysis came from samples taken from batches which were formulated weekly during the first month of the study, then monthly thereafter. (The fact that naled degrades rapidly at room temperature was offered as explanation for administration by gavage, rather than in the feed.)

Appendix II: Formulation Analysis--A typical batch of Dibrom Technical SX-1278 contained (as of November 13, 1980):

[CONFIDENTIAL BUSINESS INFORMATION]

Naled 93.3%

[redacted]

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

As reported herein, periodic sampling during the course of the rat study revealed substantial differences between BRL and Chevron in analyses of the composition. For example, on April 19, 1981, BRL assayed SX-1278 as containing 85% naled; and on January 8, 1982, only 81.1%. Subsequently, Chevron recorded an analysis of an unopened container of Lot SX-1278 as containing 93.3% naled; but a month later, another aliquot from the same batch container assayed at 84.6% naled (despite refrigeration and protection from light).

In the entry logs submitted as part of Appendix II of this Addendum, samples of the same initial batch of Lot SX-1278 sent to the performing lab (BRL) over a 2-year period varied in naled content, from approximately 90 to 94 percent.

Appendix III: Analytical Methods--Mostly developed by Chevron for use specifically with Dibrom formulations.

Appendix IV: Sample Transmittal Forms/Analytical Data--Recorded are the raw data from samples analyzed periodically by BRL, in order to check label claim of purity. Percent of label claim ranged generally from 83 to 115 percent for each of the three dosage groups, with occasional excursions higher (singular instances were reported of 130% and 180%!).

TB Conclusions

The present submission concerns additional analytical data of the specific technical (Lot SX-1278) used in the rat chronic study, S-1802. S-1802 was initially evaluated as CORE-SUPPLEMENTARY data because the study report did not provide:

1. A rationale for gavage administration;

2. Evidence that the HDT approached an MTD;

3. Individual clinical data;

4. Sufficient gross pathology; and

5. An explanation for increased mortality in controls.

(See DER attached to the memorandum: Mauer to Miller, December 20, 1984, TB Doc. No. 004128.)

Subsequently, Chevron responded to this assessment by submitting:

1. A 28-day range-finding study conducted at the same lab, BRL (not included in the original submission), supporting the dosage selection for the chronic study.

2. A dietary stability analysis of Dibrom Technical incorporated in standard rodent feed, showing that the chemical degrades rapidly at room temperature (half-life of 1.5 days at 21 °C), irrespective of concentration, thus justifying the use of gavage administration.

3. Four acute oral studies comparing the carriers, carboxymethycellulase (CMC) and corn oil, which indicated increased toxicity of CMC formulations.

Since the major issue of the MTD was resolved to the Agency's satisfaction, as were the remaining minor deficiencies by acceptable explanations in the company's rebuttal, this rat chronic study (S-1802) was subsequently upgraded to CORE-MINIMUM for both chronic toxicity as well as oncogenicity (Memorandum: Mauer to Miller/Otakie, June 28, 1985 , TB Document No.004521).
